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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
SULLIVAN, DANIEL M

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 09/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/516,310	LIN ET AL.	
	Examiner	Art Unit	
	Daniel M Sullivan	1636	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 27 August 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1.☒ A Notice of Appeal was filed on *27 August 2003*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2.☒ The proposed amendment(s) will not be entered because:

(a) ☒ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see Note below);

(c) ☒ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: *See Continuation Sheet*.

3.☐ Applicant's reply has overcome the following rejection(s): _____.

4.☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5.☒ The a)☒ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Continuation Sheet*.

6.☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7.☒ For purposes of Appeal, the proposed amendment(s) a)☒ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: _____.

Claim(s) objected to: _____.

Claim(s) rejected: *6-15,34-38*.

Claim(s) withdrawn from consideration: *16-26,32,33*.

8.☒ The proposed drawing correction filed on *27 August 2003* is a)☒ approved or b)☐ disapproved by the Examiner.

9.☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10.☐ Other: _____

Continuation of 2. NOTE: The claims have been amended such that they are no longer directed to a method of importing a biologically active molecule into a cell, but are instead directed to a method of importing a peptide, polypeptide or protein into a cell. As the peptides of the claims are no longer limited to being biologically active, the scope of the claims is different from the scope of the claims considered in prosecution and examination would require a new search. Furthermore, claims that encompass to a method of importing a peptide, polypeptide or protein which does not have biological activity raise new issues with regard to the "how to use" requirement of 35 U.S.C. §112, first paragraph.

It is also noted that this application contains claims 16-26 and 33 drawn to an invention nonelected with traverse in the response to the restriction requirement. A complete reply to a final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01..

Continuation of 5. does NOT place the application in condition for allowance because: First, it is noted that the proposed amendments to the claims, had they been entered, would overcome the following: objection to claim 6; the rejection of claims 6-10 and 34-38 under 35 U.S.C. §112, first paragraph, as containing limitations that are not supported by the originally filed disclosure; the rejection of claims 6-10 and 34-38 under 35 U.S.C. §112, first paragraph, as lacking adequate descriptive support for "an antigenic polypeptide" and "a portion of a protein"; and the rejection of claims 6-10 and 34-38 under 35 U.S.C. §112, second paragraph, as indefinite.

-Rejections under 35 U.S.C. §112, first paragraph, (enablement):

Applicant's arguments regarding enablement of the claims are first directed to the Examiner's statements regarding targeting of the biologically active molecule. Applicant argues that, contrary to the Examiner's assertion, avoiding systemic importation into all cells is not critical to the invention. Applicant cites teachings from the specification which indicate that targeting of the biologically active molecule might be achieved by various means and does not require some means to prevent importation of the molecule into all cells. This argument has been fully considered but is not found persuasive because the claims clearly encompass delivery of biologically active molecules such as toxin polypeptides, which the skilled artisan would expect to require targeting to have therapeutic utility. The Examiner acknowledges that some embodiments of the claimed invention would not require targeting selected cells for therapeutic effect, as demonstrated by the showings in the Declaration of Dr. Hawiger. However, given that the claims are directed to methods of using widely divergent biologically active molecules, including molecules that would require targeting to selected cells to be used therapeutically, the showings of the Declaration do not support enablement for the full scope of the claimed subject matter.

In response to the Examiner's assertion that undue experimentation would be required to practice the method using the broad scope encompassed by the importation competent signal peptide of the claims, Applicant cites a general teaching from the specification indicating that the importation competent signal peptide is about 10-50 amino acid residues and contains a hydrophobic, lipid-soluble portion (typically about 55-60% hydrophobic residues). Applicant argues that, in view of these teachings and teachings from the art as to how one could assay for the activity of an importation competent signal peptide, the experimentation required to practice the invention using the full scope of importation signal peptides would be routine. This argument is not persuasive because it fails to take into account the tremendous number of peptides that would have to be assayed for activity. Even if the structural features set forth in the specification were taken as absolute limitations on the importation competent signal peptide of the claims (in fact, they are only suggested as possibly relevant features) the limitations would be common to millions of peptides, only a small fraction of which would have the activity of an importation signal peptide. With regard to claims that comprise broad generic limitations, the standard for enablement is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. Atlas Powder Co. v. E.I. du Pont de Nemours & Co (224 USPQ 409, 414; hereinafter Atlas). Further, Atlas provides, "if the number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention, the claims might indeed be invalid" (page 414). Applicant's arguments fail to take into account the enormous scope of the importation competent signal peptide of the claims. Because determining which embodiments that were conceived, but not yet made, would be inoperative or operative would clearly require expenditure of more effort than is normally required in the art, practicing the full scope of the claimed method would require undue experimentation.

-Rejections under 35 U.S.C. §112, first paragraph, (possession):

In response to the Examiner's arguments of record regarding written description for the method as it broadly encompasses using any importation signal peptide, Applicant asserts that: (1) the specification indeed provides an adequate written description of the importation competent signal peptides to be used in the claimed method, (2) notwithstanding this, the specification need not provide a written description of the importation peptides to be used in the claimed method because it is only the claimed method itself that must be described, and (3) the specification need not provide a written description of the importation competent signal peptides to be used in the claimed method because the peptides are only involved in making and using the claimed method and are not the claimed method itself.

To support the first assertion, Applicant particularly cites the Written Description Guidelines (66 Fed. Reg. 1,099 (Jan. 5, 2001)) and Enzo Biochem. V. Gen-probe, 296 F.3d 1316, 1324 (Fed. Cir. 2002). Applicant states: "The standards embodied in the Written Description Guidelines in general, and in Example 16 of the Synopsis of Guidelines in particular, have recently been adopted by the Federal Circuit as valid for the analysis of compliance with the written description requirement...Enzo II states that "it is not correct...that all functional descriptions...fail to meet the written description requirement." Id. at 1324. Thus, a claim to method that includes the step of administering to the subject a complex comprising a peptide, polypeptide, or protein linked to a mammalian hydrophobic importation competent signal peptide as functionally and structurally defined by the specification (e.g., at page 10, line 20, through page 21, line 16), is adequately described even in the absence of description of the structure-function correlation between specific amino acids and the importation function of the signal peptide, as required by the Office Action" (page 11).

These arguments have been fully considered but are not found persuasive because they mischaracterize the statements found in Enzo and the Written Description Guidelines. The statement from Enzo cited by Applicant is immediately followed by, "[i]n its

Guidelines, the PTO has determined that the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant
identifying characteristics ... i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure" (emphasis added in Enzo). Citing Example 16 of the Written Description Guidelines, the court adds, "the PTO would find compliance with § 112, 1, for a claim to an 'isolated antibody capable of binding to antigen X,' notwithstanding the functional definition of the antibody, in light of 'the well defined structural characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that the antibody technology is well developed and mature.'" (emphasis added). Thus, the court clearly indicates that, contrary to Applicant's assertion, a recitation of functional characteristics alone does not provide adequate written description for a molecule. Instead, the statements made in Enzo and the Written Description Guidelines, when viewed in context, provide that a recitation of function must be "coupled with a known or disclosed correlation between function and structure". In contrast to the antibody of Example 16 of the Synopsis of Guidelines referred to in Enzo, the instant importation competent polypeptide does not have well defined structural characteristics and neither the art nor the specification disclose a correlation between function and structure.

Next, Applicant asserts that a claim to a method does not require description of the structure of compounds used in the method. Applicant states, "the written description of a method invention requires description only of the acts to be performed (because a method (e.g., one or more acts) is what the invention is)" (page 12). This argument has been fully considered, however it is the Examiner's position that a description of a method of using an importation competent signal peptide must describe that which is being used in the method. Applicant seems to be arguing that a method of delivering a biologically active molecule into a cell need not describe the active agent used in delivering said biologically active molecule; that a recitation of function in the context of a positive process step meets the written description requirement of 35 U.S.C. §112, first paragraph. By this reasoning, a claim to a method of curing cancer comprising administering an agent that cures cancer also meets the written description requirement. Applicant argues that nothing in the statute or the case law requires a written description of anything other than the claimed invention for compliance with the written description requirement. While the Examiner accepts this general premise, there is nothing to suggest that a description of the materials used in a method is irrelevant to the description of the method itself. In contrast, it is the Examiner's position that claims directed to a method of delivering an agent are not adequately described if the skilled artisan could not envision what is being delivered.

Next, Applicant argues that the requirement that the manner and process of making and using the claimed invention be described is not part of the written description requirement. Applicant discusses the case law establishing that the written description requirement of 35 U.S.C. §112, first paragraph, is distinct from the enablement requirement, which is acknowledged by the Examiner. However, the Examiner maintains that a description of a method of using a product must describe the product being used in order to meet the written description requirement. The claims recite a single process step (i.e., administering to the subject...). Applicant seems to be arguing that the invention is adequately described, even if the importation competent signal peptide is not, because the specification describes the act of administering. However, it is the structure of the importation competent signal peptide itself, not administering, that dictates importation of the biologically active molecule. Surely it cannot be the case that a description of a method of delivering a bioactive molecule into a cell need not describe that which actually delivers the bioactive molecule into a cell. Applicant then goes on to reiterate the argument that a description of a process "need only describe the act to be performed" (page 13). These arguments are addressed herein above.

Finally, Applicant asserts that identification of additional importation competent signal peptides does not implicate the written description requirement requirements of written description. Applicant argues, "the claim requires that the peptide, polypeptide, or protein be imported into the cell of the subject. This is an effect of the method, not a step of the method. Obtaining this effect is solely an issue of enablement, not written description. The effect is not a step or act required to perform the method, it is only a result that those of skill in the art must be able to obtain" (page 14). However, it is the Examiner's position that the step or act of administering is not fully described without a description of what is being administered. The claim is directed to a method of importing a biologically active molecule into a cell in a subject. Applicant is arguing that a description of the act of administering adequately describes this method even though the act itself is generic to all methods of treatment and, in and of itself, does not generally result in importation of a biologically active molecule into a cell. It is unclear how merely describing an action that does not result in a biologically active molecule being imported into a cell fully describes a method of importing a biologically active molecule into a cell. Applicant further argues, "how to make the importation competent signal peptides is at most only an aspect of how to 'make' the claimed method because the materials to be used in a method are arguably part of 'making' such a method. Making the materials used in a claimed method is clearly not the method itself or a step in the method" (page 15). This argument is not found persuasive because the basis for the written description rejection is that the specification does not describe the importation competent signal peptide of the claims (the "how to make" requirement has been addressed in previous Office Actions and herein above with regard to enablement under 35 U.S.C. §112, first paragraph). For reasons also provided in previous Office Actions and herein above, the claimed method of using an importation competent signal peptide as a whole is not adequately described in the absence of a description of the importation competent signal peptide itself. Thus, Applicants arguments, when considered individually and as a whole, are not found persuasive and the claims stand rejected under 35 U.S.C. §112, first paragraph, as lacking adequate written description for the claimed subject matter..

JAMES KETTER
PRIMARY EXAMINER